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# Synovial sarcomas usually metastasize after >5 years: a multicenter retrospective analysis with minimum follow-up of 10 years for survivors

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**Background:** Synovial sarcoma (SS) is a malignant soft tissue sarcoma with a poor prognosis because of late local recurrence and distant metastases. To our knowledge, no studies have minimum follow-up of 10 years that evaluate long-term outcomes for survivors.

**Patients and methods:** Data on 62 patients who had been treated for SS from 1968 to 1999 were studied retrospectively in a multicenter study. Mean follow-up of living patients was 17.2 years and of dead patients 7.7 years.

**Results:** Mean age at diagnosis was 35.4 years (range 6–82 years). Overall survival was 38.7%. The 5-year survival was 74.2%; 10-year survival was 61.2%; and 15-year survival was 46.5%. Fifteen patients (24%) died of disease after 10 years of follow-up. Local recurrence occurred after a mean of 3.6 years (range 0.5–14.9 years) and metastases at a mean of 5.7 years (range 0.5–16.3 years). Only four patients were treated technically correctly with a planned biopsy followed by a wide resection or amputation. Factors associated with significantly worse prognosis included larger tumor size, metastases at the time of diagnosis, high-grade histology, trunk-related disease, and lack of wide resection as primary surgical treatment.

**Conclusions:** In SS, metastases develop late with high mortality. Patients with SS should be followed for >10 years.

**Key words:** follow-up study, metastasis, sarcoma, sarcoma/surgery, soft tissue neoplasms, synovial sarcoma

## introduction

Synovial sarcoma (SS) is a high-grade, malignant soft tissue sarcoma accounting for 5%–10% of soft tissue sarcomas [1–3]. After rhabdomyosarcoma, SS is the most common soft tissue sarcoma in children, adolescents, and young adults [1]. The term 'SS' is derived from the morphological similarity to the embryonic synovialis [2, 3] and is often misinterpreted to mean that the tumor originates from synovial tissue, which is not the case [3–5]. SS has been proposed to originate from myogenic cell lines [5] and occurs in soft tissues almost anywhere in the body, most frequently in the lower (62%) and upper (21%) extremities [6, 7]. Histologically, these tumors are classified as biphasic, monophasic (purely epithelioid or fibroblastic), or poorly differentiated [8].

No consensus has been reached regarding important prognostic factors. Some studies report tumor grade as the most important prognostic indicator, while others regard all SS

as high grade and do not differentiate between grade 2 and grade 3 tumors [9, 10]. The prognostic impact of SYT–SSX fusion type continues to be a matter of debate [10–13]. Two large multi-institutional series reported conflicting results regarding the predictive role of SYT–SSX fusion type [9, 10].

SS is associated with local recurrence and distant metastases. Metastases occur in 50%–70% of cases. Since these tumors grow slowly, they have a high incidence of late metastases [1], as reflected in the difference between 5-year and 10-year survival [14]. Slow tumor growth and the apparent harmlessness of symptoms often lead to late referral to a tertiary referral center. Consequently, diagnosis and therapy are delayed, and inadequate surgery further reduces the effectiveness of therapy.

The current standard treatment is wide resection followed by polychemotherapy with or without irradiation [6, 15–17]. Regional lymph nodes also should be removed [18]. Neoadjuvant chemotherapy is a matter of debate. Initial surgical treatment with adequate surgical margins by surgeons experienced with sarcomas, preferably at specialized centers,

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should be considered to improve local control, outcome, and survival [16].

To our knowledge, currently no long-term study of the outcome of SS has been published. Although individual cases with longer follow-up have been reported, no study has a defined minimum follow-up of 10 years. Here, we investigated the extent to which individual clinical tumor-specific factors as well as surgical approach affect the outcome of patients with SS with at least 10-year follow-up.

## patients and methods

Sixty-two patients (26 men and 36 women) treated from 1968 to 1999 in the Swiss tumor centers of Basel, Bern, Geneva, Lausanne, and Zürich were included in this study with approval of the ethical review board. Written consent was obtained for participation in the study, which was conducted under the guidance of the Orthopaedic Department of the Children's University Hospital in Basel (AHK, BMS, and FH) with the participation of the Institutes of Pathology in Basel (GJ), Lausanne (LG), Zurich (ARvH), the Department of Orthopedic Surgery in Bern (FMK and KAS), University Hospital Balgrist Zurich (GUE and BF), Orthopedic University Hospital Lausanne (EM), and the Pediatric Orthopedic Department of the Children's University Hospital in Geneva (AK).

Patient and tumor data were collected from records of the participating hospitals and pathological institutes and through clinical and radiological follow-up examinations. All living and deceased patients with histological diagnosis of SS with known treatment modalities of the primary tumor and follow-up of at least 10 years (diagnosed before 1999) were included. The median follow-up of all patients was 11.4 years [range 0.3–27.6 years, interquartile range (IQR) 5.0–16.3 years]; that of living patients was 17.2 years (range 10.1–27.6 years, IQR 12.4–21.8 years); and that of dead patients was 7.7 years (range 0.3–19.6 years, IQR 2.6–11.3 years). Surviving patients without regular oncological follow-up ( $n = 10$ ) were invited for clinical examination with magnetic resonance imaging (MRI) of the original tumor site, chest X-ray, and, in case of amputation, sonography of the regional lymph nodes.

Retrieved information included age at diagnosis, sex, tumor localization, presence of metastases at diagnosis, tumor size ( $\leq 5$  versus  $> 5$  cm), histological subtype (biphasic versus monophasic), histological tumor grade (according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system) [19, 20], fusion type (SYT–SSX1 versus SYT–SSX2), treatment modalities, and tumor margins.

Tumors were classified as limb based and trunk related. The exact size of the primary tumor was available for 59 patients. In two patients, only the tumor size category of  $< 5$  cm was available. In one patient, information regarding the size of the primary tumor was not available. In addition, according to the tumor stage at diagnosis, SS was categorized as localized or metastatic disease.

The histological typing and subtyping was carried out with hematoxylin- and eosin-stained slides according to the 2002 World Health Organization classification for bone and soft tissue tumors [8]. Histological specimens were reinvestigated by two pathologists (LG and GJ). All tumors with reference to glandular structures were, regardless of the amount of glandular tissue, classified as a biphasic SS, as well as those with predominantly epithelial structures. Monophasic SS showed the predominant presence of spindle cells, round cells, or a combination of both. Poorly differentiated tumors showed a high proportion of cellularity, high-grade nuclear features, numerous mitoses (10/10 high-power fields), and partly necrotic portions [8]. Mitotic activity and tumor necrosis were used to classify tumors according to the current FNCLCC grading system as previously described [11, 21]. In cases in which paraffin blocks were available ( $n = 43$ ), these were submitted for molecular analysis.

Forty-three cases were analyzed for SYT–SSX fusion type at the University Institute of Pathology of Lausanne using reverse transcriptase–PCR as previously described [11, 22]. Nineteen cases were excluded from this analysis because histological specimens were unavailable of which 13 had been previously destroyed.

Surgical treatment was defined as technically correct if the biopsy was followed by a wide resection or amputation (adequate treatment). Nonplanned wide resection (without biopsy) was considered adequate but technically incorrect, and simple excisions or marginal resections were considered inadequate. Patients with metastases at diagnosis ( $n = 4$ ) were excluded from the analysis of technically correct/incorrect local treatment because of their predisposal toward an adverse outcome independent of local therapy to the primary tumor.

For data input and all numerical and graphical evaluations, we used the statistical software package, SPSS (Statistical Product and Services Solutions, version 17.0; SPSS Inc., Chicago, IL). In the statistical analysis, the above-mentioned variables were examined with regard to their prognostic significance. The description of steady end points used the median, first and third quartile, and minimum and maximum. The description was based on categorical end points of absolute and relative frequencies. The method of Kaplan and Meier was used for survival analysis [23]. In addition to overall survival (OS), we analyzed local recurrence-free survival (LRFS) and metastases-free survival (MFS) as a function of various clinical parameters. Comparisons were tested for statistical significance using the log-rank test [24]. The origin for the calculation of OS, LRFS, and MFS was defined as the time of histological diagnosis. The interval for LRFS was the time between diagnosis and local recurrence. MFS covered the period between diagnosis and occurrence of metastases. For MFS, the first occurrence of metastases regardless of location was defined as an event. In patients with metastatic disease at diagnosis, tumor stage had a greater influence than other prognostic factors. Therefore, these patients ( $n = 9$ ) were not included in the statistical analysis of LRFS and MFS. Patients with other causes of death were censored at the time of death. The results of significance tests were expressed in  $P$  values, with  $P < 0.05$  indicating statistical significance.

## results

Patient and tumor data are summarized in Table 1. Mean age at diagnosis was 34.5 years (range 6–82 years). At the time of last follow-up, 24 patients (39%) were alive and 38 patients (61%) were deceased of which 2 died of nontumoral causes (stroke and aspiration pneumonia) 50 and 57 months after diagnosis. At the time of last follow-up, 22 patients showed no evidence of disease and 2 patients were alive with tumor. Fifteen patients (24%) died of disease after 10 years of follow-up.

Of 47 patients with primary tumors of the limbs, 12 (25%) had tumors of the upper extremity and 35 (75%) of the lower extremity. All trunk-related SS ( $n = 15$ , 24%) were tumors of the body wall. There were no visceral SS. Patients with metastatic disease at diagnosis ( $n = 9$ ) had significantly worse outcome than patients with localized disease ( $n = 53$ ) ( $P < 0.001$ ; Figure 1).

Metastases occurred in 29 patients (47%), and median time to occurrence was 4.5 years (mean 5.9 years, range 0.5–16.3 years, IQR 2.4–8.1 years). Distant metastases were mainly located not only in the lungs (79%) but also in the regional lymph nodes (11%) and chest wall and abdomen (7%). In one case, metastases were located in the kidney and pancreas, and in another case, in the brain and lungs.

**Table 1.** Patient data and OS for 62 patients with synovial sarcoma

	All patients		OS (%)			P
	n	%	5 Year	10 Year	OS	
All			76	63	38.7	
Sex						
Male	26	42	81	66	42	0.45
Female	36	58	72	61	36	
Age, years						
0 ≤ 20	13	21	77	61	61	0.13
> 20 ≤ 40	24	39	87	71	42	
> 40 ≤ 60	20	32	70	60	25	
>60	5	8	40	40	20	
Tumor site						
Limb based	47	76	81	72	47	0.001
Trunk related	15	24	60	33	13	
Tumor size (cm)						
≤5	30	51	87	71	55	0.01
>5	31	49	63	53	23	
Unknown	1					
Histologic type	50					
Biphasic	22	44	64	59	36	0.5
Monophasic	28	56	82	71	46	
Unknown	12					
Mitoses/10 hpf	43					
0–9 (score 1)	25	58	100	92	60	0.000
10–19 (score 2)	10	23	70	50	30	
>19 (score 3)	8	19	12.5	0	0	
Necrosis	43					
≤50% (score 1)	32	74	91	84	53	0.000
>50% (score 2)	11	26	36	18	9	
Unknown	20					
Tumor grade	43					
Grade 2	32	74	97	84	56	0.000
Grade 3	11	26	18	0	0	
Unknown	19					
Fusion type	43					
SSX1	30	71	80	70	47	0.2
SSX2	13	29	69	62	31	
Treatment	61					
Only S	20	33	85	80	55	0.2
S + R	7	11	71	57	29	
S + C	14	23	64	57	36	
S + C + R	20	33	76	52	29	
Type of resection						
Intralesional	17	27	71	53	18	0.01
Marginal	26	42	77	62	27	
Wide	10	16	80	80	80	
Amputation	9	15	78	67	67	
Biopsy in center						
Yes	19	32	63	58	26	0.2
No	41	68	83	66	46	
Unknown	2					
Adequate treatment						
Correct	4	7	75	75	75	0.2
Not correct	54	93	81	67	39	
Excluded	4					

Significant *P*-values are given in bold.

C, chemotherapy; hpf, high-power field; OS, overall survival; R, radiotherapy; S, surgery.

Local recurrence occurred in 29 patients (47%). The average time to local recurrence was 4.1 years (range 0.5–14.9 years, IQR 1.0–7.2 years). In eight patients (28%), local recurrence occurred after >5 years, with as many cases (14%) occurring between 5 and 10 years and after >10 years (14%).

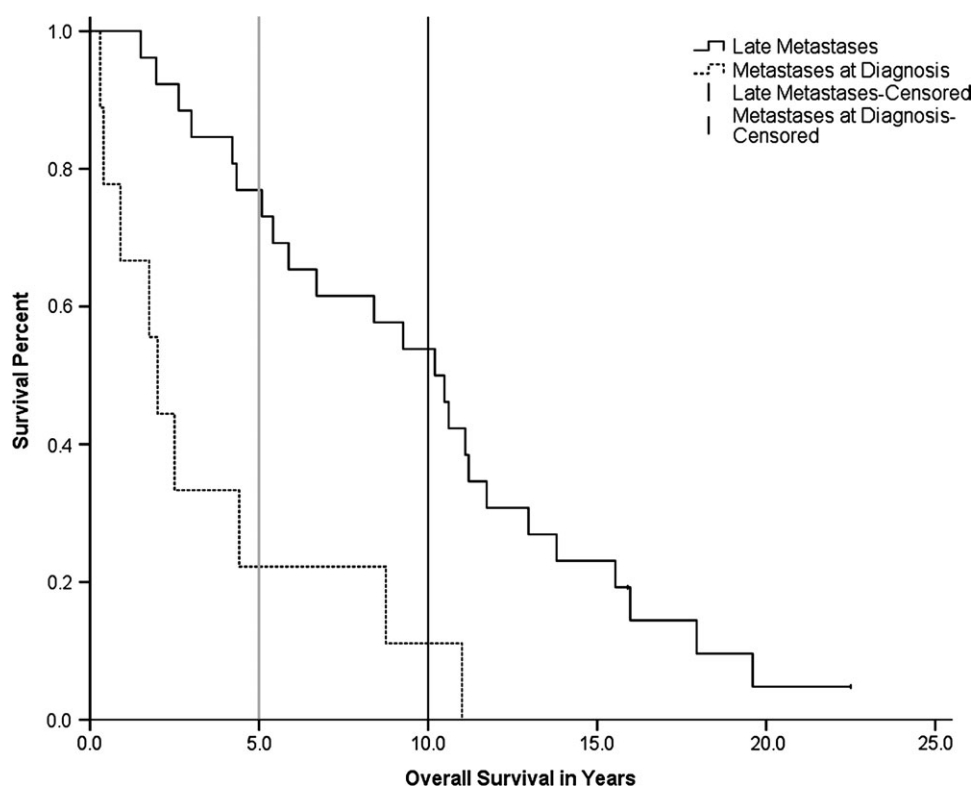
Information regarding all treatment modalities was available for 61 of 62 patients. Of these, 20 patients (33%) had surgical treatment only, 7 patients (11%) had surgery and radiotherapy, 14 patients (23%) had surgery and chemotherapy, and 21 patients (33%) received all three treatment modalities. In terms of adjuvant radiation, 28 patients (45%) received some form of radiation therapy. Four patients received preoperative radiation with a median dose of 50 Gy (range 40–60 Gy), and 24 patients received postoperative radiation with a median dose of 56.8 Gy (range 45–64 Gy). All patients with postoperative radiation had the therapy because of insufficient margins or after resurgery because of intralesional resection. Thirty-five patients (56.4%) received chemotherapy at some time in the course of treatment. The most common regimen was doxorubicin and ifosfamide in 24 of 35 patients (69%), in 3 of those combined with other additional drugs. The other 11 patients different regimen with diverse combinations of drugs were used from the different oncological teams.

In 19 patients (31%), a biopsy was obtained in the referral center; in 41 patients (66%), treatment occurred at an outside facility before referral; and for 2 patients (3%), no information about the place of primary treatment was available. Almost half of tumors ( $n = 26$ , 42%) were marginally resected. In 17 cases (27%), resection was intralesional. In 10 patients (16%), biopsy was followed by wide resection and in 9 cases (15%), by amputation as a primary procedure. For one patient, no information was available on the type of first resection. For only four patients (7%), complete diagnostic and primary treatment was made in a referral center.

Survival analysis results are summarized in Tables 1 and 2. The 5-year survival was 74.2% ( $\pm 6\%$ ); 10-year, 61.2% ( $\pm 6\%$ ); and 15-year, 46.5% ( $\pm 7\%$ ) (Figure 2). OS was 38.7%. Mean MFS ( $n = 53$ ) was 11 years (range 0.5–27.6 years, IQR 4.2–16.2 years). The 5-year MFS was 72% ( $\pm 6\%$ ) and 10-year MFS, 60% ( $\pm 7\%$ ).

The majority of patients were 20–40 years old (39%). While OS appeared to decrease with age, there was no significant relationship between age and OS ( $P = 0.13$ ), LRFS ( $P = 0.2$ ), or MFS ( $P = 0.9$ ). There was no significant difference in OS in patients of pediatric age (<18 years) ( $n = 12$  in comparison to adults) ( $P = 0.182$ ). In these patients, 5-year survival was 75% ( $\pm 14\%$ ) and 10-year survival was 58% ( $\pm 14\%$ ) compared with adult patients 72% ( $\pm 6\%$ ) and 58% ( $\pm 7\%$ ). There was also no significant difference in MFS ( $P = 0.887$ ) and LRFS ( $P = 0.321$ ). In addition, there was no significant relation between sex and OS ( $P = 0.45$ ), LRFS ( $P = 0.1$ ), and MFS ( $P = 0.1$ ).

In patients with limb-based tumors or trunk-related SS, 5-year survival rates were higher than 10-year survival rates. Patients with tumors in the extremities had significantly better OS than patients whose tumors were located on the trunk ( $P = 0.001$ ; Figure 3). There was a significant trend for better outcomes in limb-based SS based on local recurrence ( $P = 0.06$ ) or distant metastases ( $P = 0.07$ ).



**Figure 1.** Patients with late metastases had significant better overall survival than those with metastases at diagnosis ( $P < 0.001$ ).

Patients with tumors of diameters  $>5$  cm had significantly worse OS ( $P = 0.01$ ; Figure 4) and LRFS ( $P = 0.04$ ) than those with tumors  $\leq 5$  cm in diameter. However, distant metastases were not significantly associated with tumor size ( $P = 0.1$ ).

Information on the histological subtype was available for 50 patients, and 28 SS (56%) were monophasic and 22 (44%) were biphasic. The 5-year and 10-year survival rates did not differ significantly between patients with monophasic or biphasic SS ( $P = 0.5$ ), and there was no significant relationship between histological subtype and OS ( $P = 0.5$ ), local recurrence ( $P = 0.8$ ), or distant metastases ( $P = 0.5$ ).

Data on fusion type was available for 46 patients. In 27 patients (58.7%), the tumor was positive for SSX1 and in 19 patients (41.3%) for SSX2. The 5-year and 10-year survival rates did not significantly differ with fusion type nor was the association of fusion type with OS ( $P = 0.2$ ), local recurrence ( $P = 0.053$ ), and distant metastases statistically significant ( $P = 0.1$ ).

Compared with patients with grade 2 tumors, patients with grade 3 tumors had significantly poorer prognosis in terms of OS ( $P < 0.001$ ) (Figure 5), local recurrence ( $P = 0.02$ ), and distant metastases ( $P < 0.001$ ).

There was a very high rate of technically incorrectly treated patients (93%;  $n = 54$ ). Patients who underwent wide resection ( $n = 10$ ) had a significantly better prognosis in terms of OS ( $P = 0.04$ ; Figure 6) and local recurrence ( $P = 0.001$ ) than those who did not ( $n = 52$ ). Patients with wide resection had a significantly better OS ( $P = 0.038$ ) than those with marginal resection combined with radiotherapy ( $n = 12$ ). Patients with intralesional resections compared with those with other surgical

procedures had a significantly poorer prognosis regarding OS ( $P = 0.021$ ), local recurrence ( $P = 0.055$ ), and distant metastases ( $P = 0.021$ ).

The comparison of the subgroups of patients who underwent adjuvant treatment in addition to surgery (i.e. surgery and radiotherapy, surgery and chemotherapy, surgery and radiochemotherapy) showed no significant difference in OS ( $P = 0.24$ ). Patients treated with surgery only (and therefore in a better prognostic group) had a significantly better outcome in terms of OS ( $P = 0.055$ ; Figure 7) and distant metastases ( $P = 0.012$ ) than those who received adjuvant treatment.

## discussion

The aim of this study was to identify prognostic factors and evaluate surgical treatment in terms of their influence on the long-term outcome of SS. Other than solitary cases, no published studies have a minimum follow-up of 10 years for survivors; therefore, we chose extended follow-up as the most important inclusion criterion for our study. This is especially important because of the slow growth of SS and because metastases and local recurrence are known to occur very late. Various prognostic factors including age, tumor size [11, 14, 25–28], surgical margins [11, 14], histological subtype [10, 11], tumor grade [11, 29], and fusion type [10, 11] have been identified in previous studies. The relative influence of these factors, however, is controversial. Only tumor size ( $>5$  cm) is consistently associated with a negative outcome [6, 9, 11, 14, 30, 31].

Our study has several limitations. It is retrospective, and the patient group consisted of a very heterogeneous population of

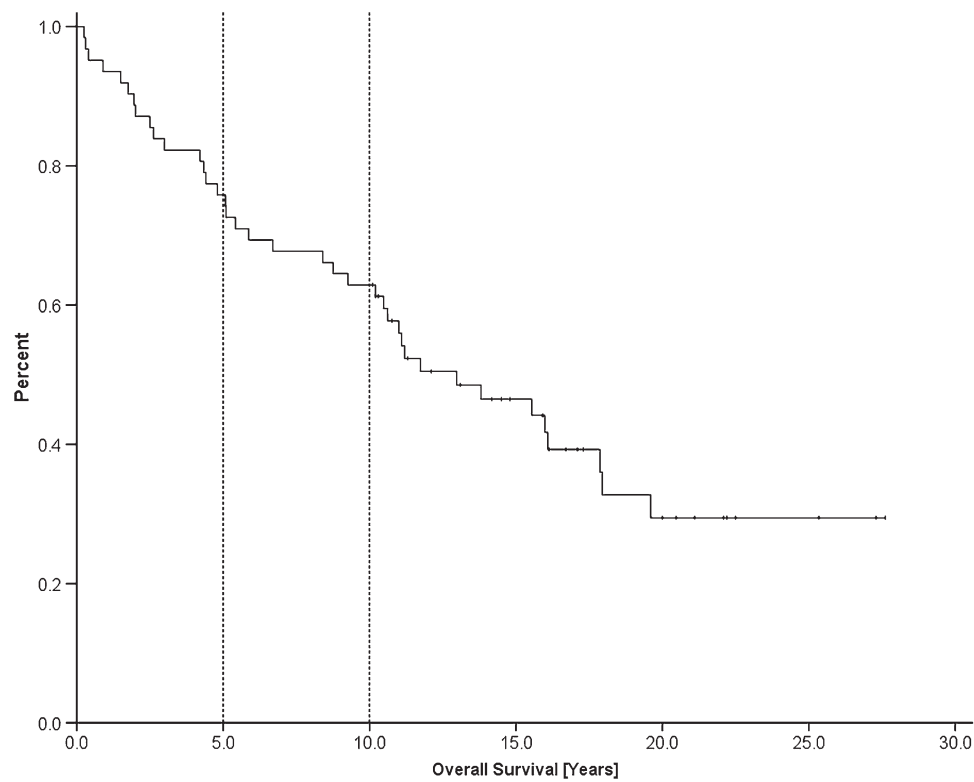


**Table 2.** Local recurrence and distant metastases in patients with synovial sarcoma

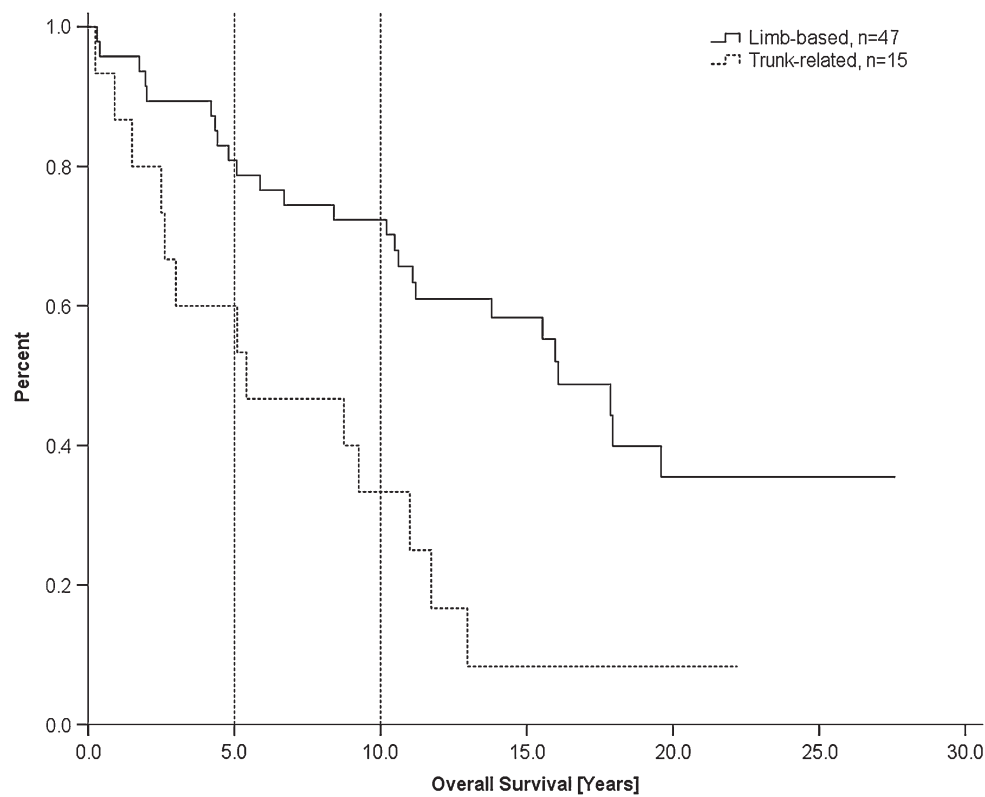
	All patients		Local recurrence (%) ( <i>n</i> = 29)			Distant metastases <sup>a</sup> (%) ( <i>n</i> = 29)		
	<i>n</i>	%	5 Year	10 Year	<i>P</i>	5 Year	10 Year	<i>P</i>
All patients			36	45		28	40	
Sex								
Male	26	42	25	30	0.1	18	23	0.1
Female	36	58	44	56		36	53	
Age at diagnosis, years								
0 ≤ 20	13	21	31	31	0.2	39	39	0.9
> 20 ≤ 40	24	39	25	41		30	39	
> 40 ≤ 60	20	32	48	56		21	53	
>60	5	8	75			0	50	
Tumor site								
Limb based	47	76	31	39	0.056	24	34	0.07
Trunk related	15	24	56	71		45	71	
Tumor size (cm)								
≤5	31	51	27	31	<b>0.04</b>	24	35	0.1
>5	30	49	49	64		35	49	
Unknown	1							
Histologic type	50							
Biphasic	22	44	26	33	0.8	33	39	0.5
Monophasic	28	56	30	38		13	27	
Unknown	12							
Mitoses/10 hpf	43							
0–9 (score 1)	25	58	20	29	<b>0.000</b>	12	21	<b>0.000</b>
10–19 (score 2)	10	23	21	21		33	47	
>19 (score 3)	8	19	83	83		75	100	
Necrosis	43							
≤50% (score 1)	32	74	28	32	0.4	16	30	<b>0.04</b>
<50% (score 2)	11	26	43	56		67	67	
Unknown	19							
Tumor grade								
Grade 2	32	74	22	29	<b>0.02</b>	16	26	<b>0.00</b>
Grade 3	11	26	45	–		67		
Unknown	19							
Fusion type	43							
SSX1	30	71	25	25	0.053	19	27	0.1
SSX2	13	29	40	60		37	55	
Treatment	62							
Only S	20	32	28	40	0.955	11	11	0.06
S + R	7	11	33	67		20	57	
S + C	14	23	39	49		45	64	
S + C + R	21	34	43	43		37	54	
Type of resection								
Intralesional	17	27	54	67	<b>0.000</b>	33	62	<b>0.05</b>
Marginal	26	42	45	57		29	42	
Wide	10	16	0	0		20	20	
Amputation	9	15	14			29	29	
Biopsy in center								
Yes	19	<b>32</b>	23	40	0.3	31	52	0.2
No	41	68	42	48		28	37	
Unknown	2							
Adequate treatment								
Correct	4	7	None	None	0.087	15	15	0.4
Not correct	54	<b>93</b>	37	47		29	42	
Excluded	4							

<sup>a</sup>Patients with distant metastases are those without primary metastases.Significant *P*-values are given in bold.

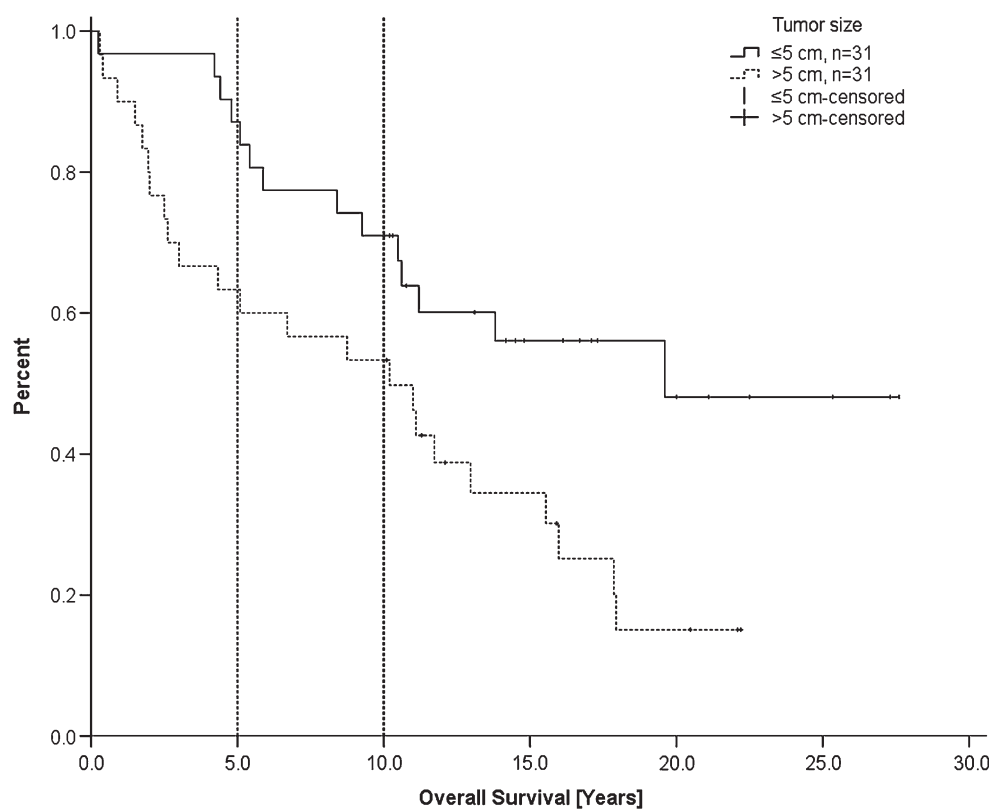
C, chemotherapy; hpf, high-power field; OS, overall survival; R, radiotherapy; S, surgery.



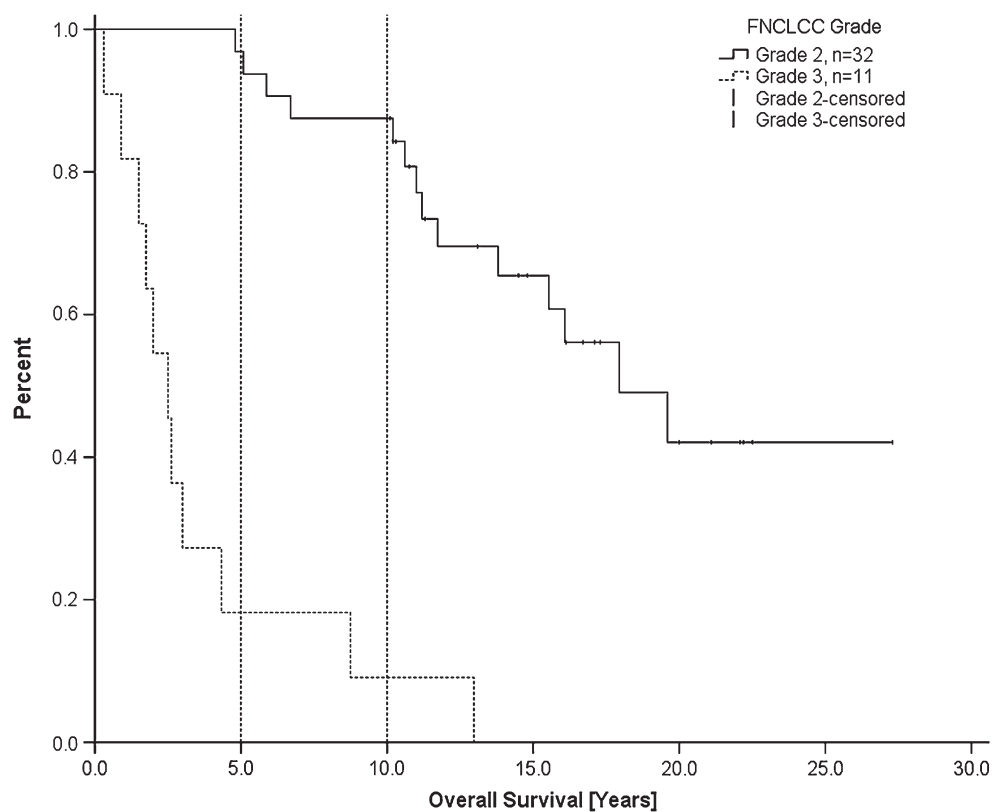
**Figure 2.** Overall survival at 5 years was 74.2% ( $\pm 6\%$ ); at 10 years, 61.2% ( $\pm 6\%$ ); and at 15 years, 46.5% ( $\pm 7\%$ ).



**Figure 3.** Overall survival according to tumor site (limb based versus trunk related),  $P = 0.001$ .

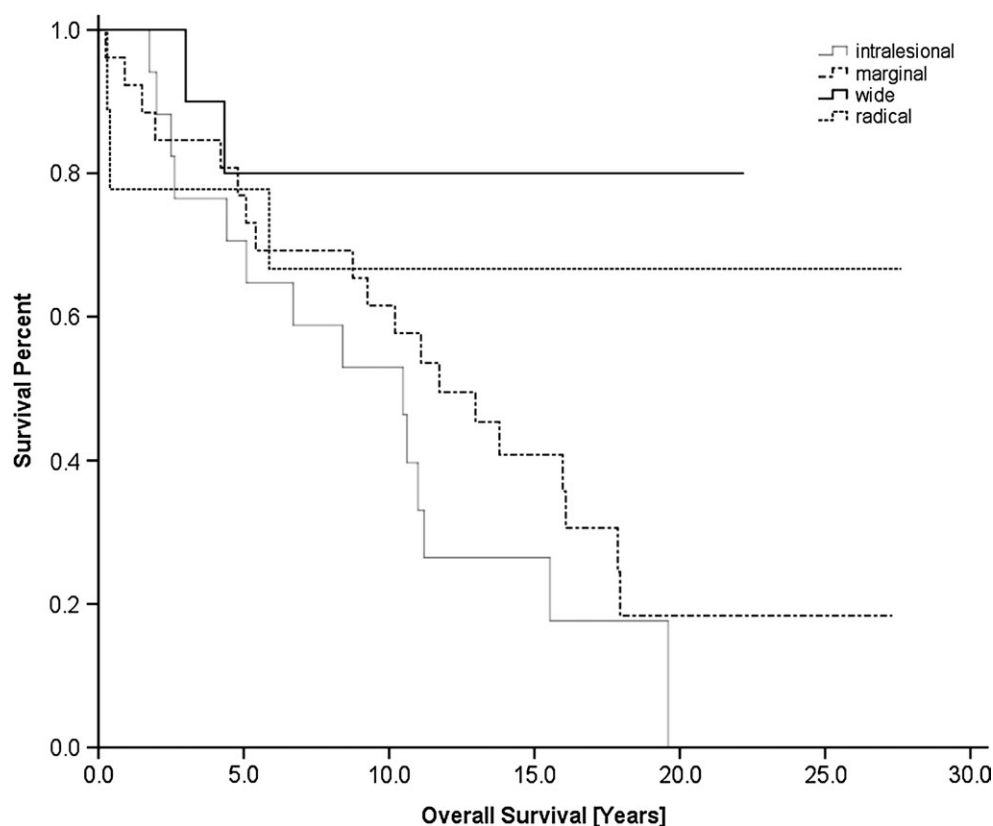


**Figure 4.** Overall survival according to tumor size ( $\leq 5$  versus  $> 5$  cm),  $P = 0.013$

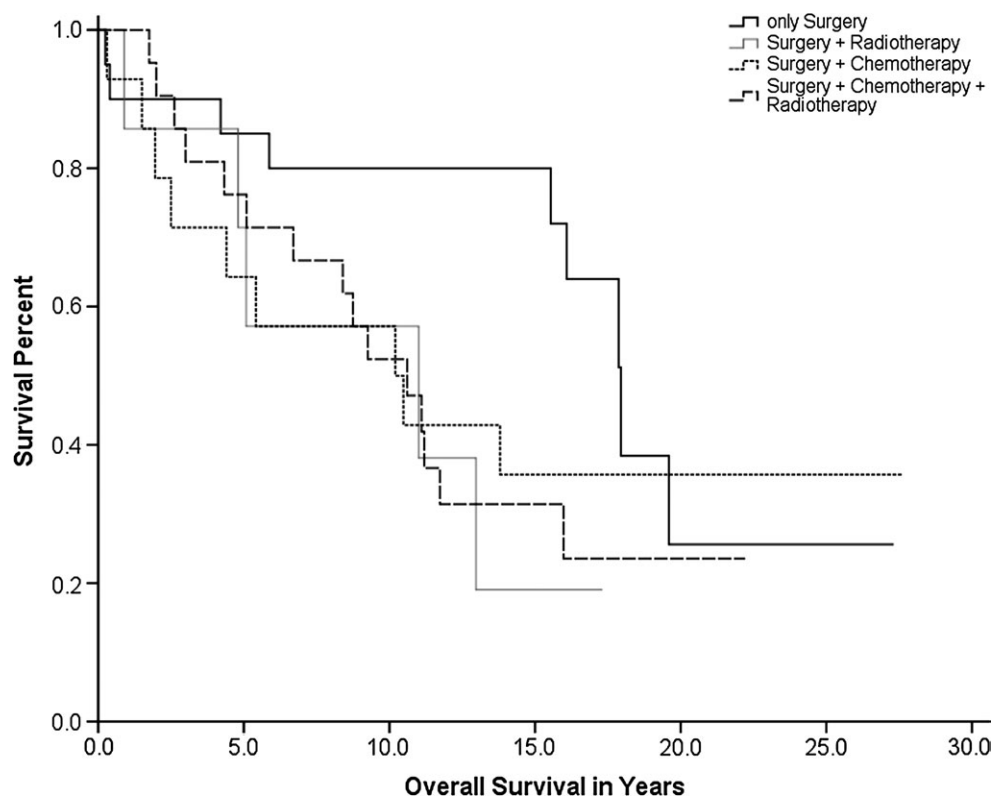


**Figure 5.** Overall survival according to histological grade (grade 2 versus grade 3),  $P < 0.001$ .





**Figure 6.** Overall survival according to the type of resection. In comparison with other types of resection, overall survival in patients with wide resection was significantly better ( $P = 0.04$ ) and overall survival in patients with intralesional resection was significantly worse ( $P = 0.021$ ).



**Figure 7.** Patients who were treated with surgery only had a significantly better prognosis in terms of overall survival ( $P = 0.055$ ) than those who received adjuvant treatment.

which many were treated outside of a tertiary referral center before their referral. Through its multicenter design, there was no agreement on surgical and adjuvant treatment modalities. The patients early in the series were diagnosed by means of histological examination without staging through modern radiologic methods such as MRI or computed tomography and without molecular verification of SYT–SSX type. For analysis of tumor size, we chose largest diameter instead of tumor volume due to a lack of available data for calculation of volume. Eight patients with minimum follow-up of 10 years were not available for follow-up examination because they had either moved to other countries or could not be found.

In the literature, 5-year survival ranges from 25% to 75% and 10-year survival from 11% to 63% [6, 10, 11, 14, 25, 26, 32–36]. In these studies, 10-year survival was extrapolated, whereas in our study with minimum follow-up of 10 years, it represents a true estimate. In the present study, 5-year survival was 75.8% and 10-year survival was 62.9%, which is in accordance with the literature. The 15-year survival was 46.5%. The difference between 10-year and 15-year survival reflects the fact that metastases in SS often occur very late, even beyond 10 years ( $n = 5$ ), and furthermore suggests that for these patients, clinical follow-up of 5 or 10 years is insufficient.

Metastases at diagnosis were a significant negative prognostic factor in our study (15% of patients,  $n = 9$ ). The literature reports metastases at diagnosis in 11%–14% of cases [10, 11, 37] and a significant correlation between metastases at diagnosis and survival [10, 11, 37].

Tumor size  $>5$  cm was a strong prognostic factor with a negative influence on OS ( $P = 0.01$ ) in our study. For tumor size, we chose cut-off values of  $\leq 5$  cm and  $>5$  cm since these achieved the best prognostic value. ten Heuvel et al. [37] and Ladanyi et al. [10] used the same cut-off values and also found a significant correlation between tumor size and survival ( $P = 0.0214$  and  $0.04$ , respectively).

In our study, neither histological subtype ( $P = 0.5$ ) nor fusion type ( $P = 0.2$ ) significantly influenced OS. The impact of fusion type on prognosis is controversial. In addition to its diagnostic meaning, a prognostic value has been ascribed to fusion type. In a pilot study, Kawai et al. [12] showed that patients with tumors of type SYT–SSX1 had significantly shorter MFS than those with tumors of type SYT–SSX2. These preliminary results were confirmed by the same authors in a large multicenter study with 243 patients [10, 12]. In accordance with our results, the relationship between fusion type and survival was not confirmed in several other studies [11, 29, 37].

Most local recurrences result from inadequate primary surgical treatment [17]. In our series, 42% of tumors ( $n = 26$ ) were resected marginally and 27% ( $n = 17$ ) of patients had intralesional resections. Only 31% of patients ( $n = 19$ ) were adequately treated with a wide resection or amputation. Only four patients were correctly treated without delay after biopsy. Patients who had wide or radical resection had a significantly better outcome in terms of OS ( $P = 0.04$ ) and local recurrence ( $P = .001$ ). Those patients in whom surgery was intralesional had a significantly poorer outcome in terms of OS ( $P = 0.021$ ), local recurrences ( $P = 0.055$ ), and distant metastases ( $P = 0.021$ ). The better outcome in patients who had surgery only compared with those with adjuvant chemotherapy/

radiotherapy in addition might represent the fact that, in those cases, the margins were usually clear and therefore additional chemotherapy and/or radiotherapy was not considered necessary.

The fact that two-thirds of patients in our study were primarily treated outside a tertiary referral center is an important problem in our country. The large number of patients ( $n = 54$ ) who underwent inadequate treatment initially is in contrast to the current recommendation that these patients need coordinated interdisciplinary treatment that is only possible in tumor centers.

## conclusion

Significant adverse prognostic factors for SS included larger tumor size, metastases at diagnosis, high histological grade, trunk-related disease, and intralesional or marginal surgery. Sex, histological subtype, and SYT–SSX fusion type were not significant prognostic factors. The high proportion of SS with technically incorrect treatment emphasizes the recommendation that the entire treatment should be carried out in an interdisciplinary tumor center from the beginning. Based on the high rate of local recurrence and metastases even after 5 and 10 years, we suggest that patients with SS be followed for  $>10$  years. For SSs, patient education and yearly follow-up for even  $>10$  years with thorough history and physical examination seem advisable to detect the common late recurrences at an early stage, when treatment might still be feasible. By reducing morbidity and limiting the extent of secondary treatment, this may also be a cost-effective strategy. Routine surveillance imaging is only of significant benefit if the risk for asymptomatic recurrence is high or if other factors make clinical assessment difficult.

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## disclosure

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